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Role of GPR109A Receptor in the Efficacy of Nicotinic Acid

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ABSTRACT: Nicotinic acid is used to treat dyslipidemia from the past few decades. Nicotinic acid has the capability to increase plasma HDL cholesterol concentration, and so it is being used as a potential pharmacological agent. Nicotinic acid has an unwanted side effect called flushing, which effect the patients compliance as this is unpleasant . With the help of receptor GPR109A for nicotinic acid it is possible to understand the underlying mechanism of action and effects of nicotinic acid, and this helped in maximizing the potential pharmacological effects of nicotinic acid and reducing the flushing side effects. GPR109A is a G protein coupled receptor which is activated by nicotinic acid (NA). The role of GPR109A receptor in the efficacy of nicotinic acid is discussed in this paper.

INTRODUCTION

Nicotinic acid has been used to treat dyslipidemia from many years and also atherosclerosis [1,2]. The antiatherosclerotic effect of nicotinic acid is observed in rabbits for the first time after the discovery of nicotonic acid capability to lower the cholesterol by Altschul [3]. Later in the other animal experiments there was a reduction of atherosclerotic lesion is seen due to nicotinic acid and its derivatives [4,5,6,7]. A combination of nicotinamide and nicotinic acid is called Niacin and vitamin B3 is used as pharmacotherapeutic agent since 1955, which makes it the oldest lipidemic drug as its discovered in the old years. Vitamin B3 plays an important role in the proper functioning of central nervous system as it works on providing neuroprotection and prevents neuronal death.

The angiographic studies first showed the antiatherosclerotic effects in humans from the use of nicotinic acid and the studies showed regression of antiatherosclerosis in coronary and peripheral arteries [8,9]. Also with the help of nicotinic acid there is reduction in the cardiovascular diseases are seen to have reduction [10]. Some recent studies showed that nicotinic acid has enhanced the effects of statin in reducing the risk of HDL issues. These studies also proved to slow down the atherosclerosis progression in patients with low levels of HDL.

Nicotinic acid is being used for more than fifty years as pharmacological agent to treat dyslipidemia and is still used as an effective strategy over serum triglycerides and to increase HDL cholesterol. In the clinical trails that were randomly conducted for the first time it is observed that niacin reduced occurrence of heart disease, by reducing the triglyceride concentrations by 27 percent and reduced the mortality rate due to CVD by 26% and myocardial infractions by 27%. Studies also proved that niacin is also able to reduce the number of angiographically documented vascular lesions and the thickness of carotid artery intima in patients with cardiovascular disease [11,12].

The improvement in the prevention of cardiovascular issues due to niacin are mainly due to its effect on lipoprotein and blood lipid and reduction in vascular inflammation along with thrombosis [13]. Some other studies recently also proved the significance of niacin modulating serum adipokine concentrations. Researcher [14] proved that in his research that by treating obese men who has metabolic syndrome, with niacin for 6 weeks increased adiponectin serum by 54%. Investigations that are done by other researchers in support of this findings further found that the increase in adiponectin in mainly due to increase in HMW form of adiponectin [15]. Effects of nicotinic acid on adiponectin serum concentration are important, as it is important biomarker of metabolic disease with insulin sensitizing, anti inflammatory properties. Adiponectin serum are usually low in obese people and are strongly associated with Cardiovascular diseases. So it is proved that niacin plays a major role in increasing adiponectin serum concentration thereby reducing CVD risk. NA has short biological halflife of 1-3 hours. Researchers [16] has developed dissolution controlled system for NA by encapsulating with natural phenolic antioxidant polymer. This approach is to achieve stable drug level in plasma with reduced fluctuations via slow drug release over an extended period of time The F4 and F5 formulations resulted in good drug release and encapsulation efficiency. But formulation F-4 showed the release percentage of 97.74% for 11 hours

whereas F-5 with 97.23% for 12 hours. The results suggested that the formulated controlled-release tablets of NA through encapsulation can be effective than the conventional dosage forms and also better patient compliance

This reduction in adipose tissue with nicotinic acid administration is due to the activation of recently identified G protein coupled receptor GPR109A. A number of agonists which includes acipimox , acifran and niacin are identified to activate the receptor. From the oxidation of fatty acids ketone body β-Hydroxybutyrate (β-OHB) is produced which is also identified as endogenous ligand of the receptor .It is proved that for niacin mediated reduction of adipose tissue GPR109A is needed but the role of GPR109A in the regulation of adiponectin secretion is not known.

MECHANISM OF ACTION OF NICOTINIC ACID

In the mitochondria Niacin will undergo biochemical reactions and forms nicotinamide. Nicotinamide adenine dinucleotide and NAD phosphate are formed from tryptophan shown in figure 1. The formed NAD and NADP are the niacin forms that are active which reduces to NAD (H) and NADP (H) and are formed as a cofactor in anabolic redox reactions and thus participates in catabolic redux reactions. Even though Niacin has been used though out many years, pleiotropic effect of it makes it difficult to grasp its mechanism of action completely. However based on certain effects and its targeted mechanism of action, the use of it in the human body are:

1. Capability of niacin in lowering lipid levels is very diverse and is under investigation. One of the mechanisms proposed was to mediate action of niacin's antilipolytic effect via nicotinic acid receptors. Another alternate mechanism which was recently discovered is the ability to speed up the intracellular degradation of Apo lipoprotein B (ApoB) by niacin, which contains lipoproteins like VLDL and LDL by inhibiting triglyceride synthesis. Niacin also decreases hepatic triglyceride synthesis by inhibiting diacylglycerol acyltransferase 2 (DGAT2). One suggested mechanism to increase the HDL cholesterol levels is to use niacin's ability to decrease the degradation of ApoA-I-containing lipoproteins and increase peroxisome proliferator activated receptor PPARγ) expression and enhances PPARγ transcriptional activity in macrophages [17]. With the help of downregulating action of Niacin's cyclic adenosine monophosphate free fatty acid levels can be lowered. By doing this, pro-lipolytic stimuli can be reduced which is an important intracellular mediator.

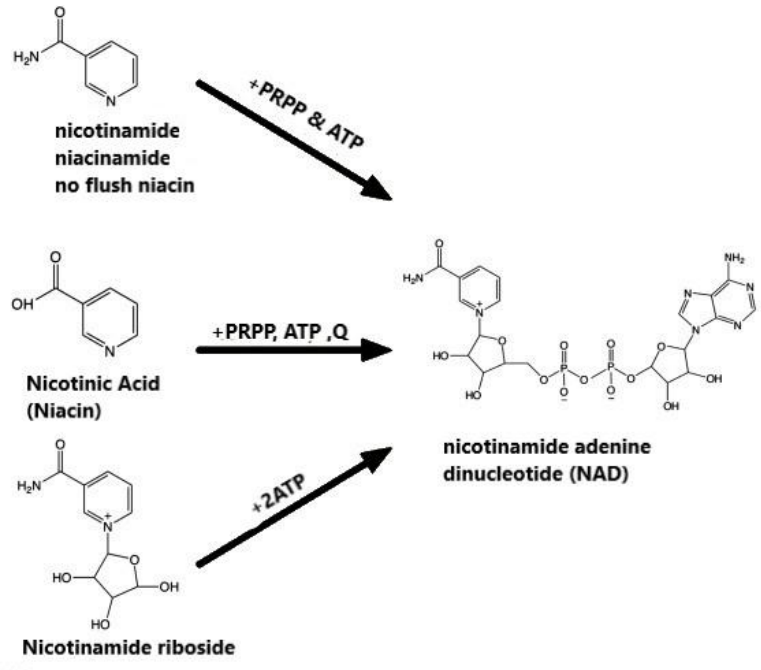


Fig 1: Formation of NAD

2. Increased fasting glycemia: Using the role of niacin's responsive G protein coupled receptor (GPRA109) and PFAs (plasma free fatty acids) this could be achieved. This research has identified relationship between resistance of insulin in muscles and high FFA, even though the details of mechanism are still yet to be discovered. When GPRA109 is stimulated by niacin it is observed to increase the local glucose uptake in vivo intestinal cells, which may contribute to loss of glycemic control [19].
3. Aging related pathologies and process: There is an inverse relationship is found between nicotinamide adenine dinucleotide (NAD) concentration vs intake of dietary niacin, even though the mechanism of action is yet to be fully

discovered. Power of cell to undergo growth and division is lost if the intracellular NAD concentrations are reduced which could lead to cell aging and death [6]. For the protection of the genome and DNA damage repair NAD dependent enzymes like sirtuin proteins and ADP-ribose and PARP continuously provide protection. With the decrease of PARP, researchers noticed increase of cancer incidence and reactive oxygen species. Also the effects of caloric restriction to extend the life span that is mediated by sirtuins are associated with aging prematurely and other disorders like Huntington and also age associated neurological disorders in the cells with defective situins [20].

4. Malignant glioma: Both in in-vivo and in-vitro niacin might exhibit glioma cell invasion. Cell migration, adhesion and polarity is carried out with the help of epithelial mesenchymal transition EMT. Even in the E-cadherin downregulation, which is an epithelial marker and upregulation of snail, and both these processes are important for the normal development of mesoderm and neural crest migration. EMT is involved. Cells are found to have EMT like processes by researcher, which not only gives the ability for them to recur but also to cause immunosuppression and cell invasion. With the help of treatment using niacin the degradation of snail, and EMT promoting transcription factor which can lead to U251 glioblastoma multiforme cell invasion, which leads to tumor invasion decrease [21,22].

NICOTINIC ACID RECEPTOR GPR109A

GPR109A which is also called as hydroxy carboxylic acid 2 receptor or also called HM74a is the receptor for nicotinic acid. The receptor GPRA109 acts as mediator in expanding repertoire of therapeutic actions that has potential [23, 24]. Gi protein coupled cell surface receptors which are expressed in adipocytes and immune cells in both rodent species and human cells, and GPRA109 belongs to this family. In human monocytes and adipocytes, the anti inflammatory effects of NA are seen [25, 26]. These effects are mediated via GPRA109 mechanisms. These observations are also recently studied in mice, which proved that NA reduces atherosclerosis progression using GPRA109 on myeloid cells which having any effect on plasma lipoproteins. This Gi protein coupled receptor is called HM74A in humans and PUMA-G in mice, which is alos helpful for cardiovascular issues as it is used to modify lipoproteins in humans. This use of NA as therapeutic agent is highly due to the GPR109A activation on adipocytes surface. In spleen and lung tissues GPRA109 and mRNA is expressed, but it is not yet clear in which cells the receptor is expressed and if it is functional. In the recent studies it is shown that interferon is able to induce receptor GPR109A in macrophages and prostaglandin E2 and D2 is stimulated in these cells. In the cells outside of adipose tissue , identification of functional GPR109A raised the question that if the there are another cell types that carry GPR109A receptors, which can also be targeted in the therapy with NA. Some of the observations done by researchers are that NA plays an important role in atherosclerosis regression in humans alongside with its capacity to act on monocyte and macrophage as we discussed earlier and this in turn regulates proteins that are associated with cholesterol efflux, which can raise important factor that NA excerpts effects via GPR109A leading to plaque regression.

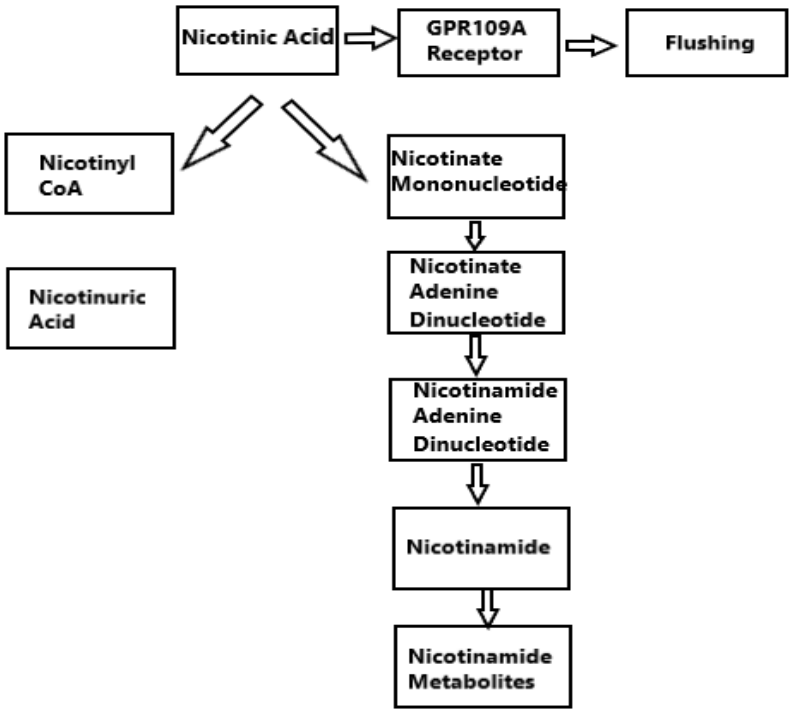


Fig 2: Nicotinic acid metabolite role in flushing

Role of GPR109A Receptor in the Efficacy of Nicotinic Acid

The effects of NA on human macrophage foam cells are tested by researcher [27,28] to explore their mechanism of action in lipid handling, and the confirmation that NA induces flushing response is mediated by GPRA10A raised some interesting doubts like whether it will be possible to get efficacy that is beneficial without flushing induced by GPR109A and it was figured that different other formulations, drugs and GPR109A ligands have induced less flushing than NA [27,28]. So, as the diversity of GPR109A is increased in the chemical aspect it is more possible that flushing is less compared to that induced by NA. Another question raised was the involvement of GPR109A which is located outside of adipose tissue can contribute to the clinical efficacy of NA due to its flushing response.

GPR109A is highly expressed in lymphoid cells. This expression profile, coupled with the observation that in murine macrophages, GPR109A is upregulated by cytokines like IFN-γ (24), may suggest a role for GPR109A in immunity and inflammation. If this is the case, then it is interesting to speculate on whether nicotinic acid achieves any of its clinical efficacy via these cell types (e.g., at the level of the atherosclerotic plaque) and not solely via the normalization of aberrant lipoprotein profiles. Furthermore, one could speculate on a degree of analogy with the mechanism of action that results in the flushing response, for example, the generation of prostaglandins following the liberation of arachidonic acid via GPR109A stimulation.

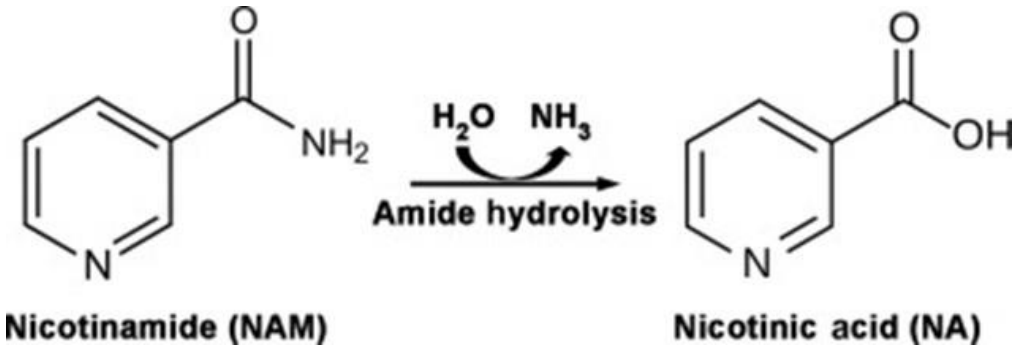
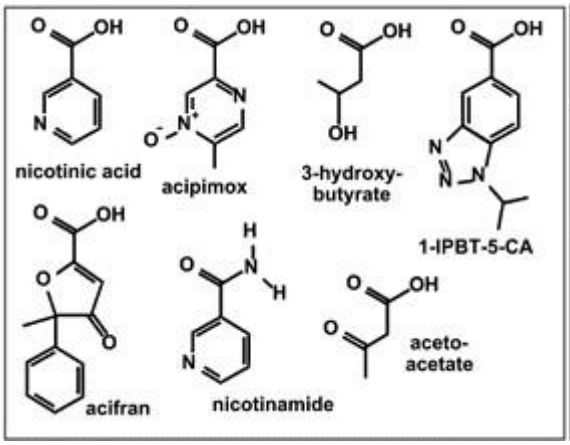


Fig 3: Niacin and transcriptome analysis in relation to the GPR109A receptor

If this functionality of GPR109A is indeed involved in the clinical efficacy of nicotinic acid, it raises further areas for investigation, which would include determination of whether the tachyphylaxis observed in the flushing response to nicotinic acid and acipimox is observed in other immune/inflammatory cell types and whether the symptomatic relief from flushing achieved by NSAID administration has detrimental effects on some aspects of the efficacy of GPR109A agonists. NSAID treatment will not effect the lipoprotein changes that are happened with nicotinic acid, which possibly suggests the direct involvement of event mediated by GPR109A .



	EC_{50} (μM)	
	GPR109A	GPR109B
nicotinic acid	0,1	>100
acipimox	5,1	>100
3-hydroxybutyrate	750	25 000
1-IPBT-5-CA	>1000	0,4
acifran	1,2	7
nicotinamide	inactive	inactive
acetoacetate	>25 000	25 000

Fig 4: Structures and properties of ligands GPR109A and GPR109B

Nicotinic acid will show several side effects which might be harmless. The most common side effect of nicotinic acid is cutaneous vasodilation, most commonly in the upper half of body and the face. This effect would last for one to two hours after nicotinic acid is taken orally. This cutaneous reaction is called as flushing. This effect flushing effect the compliance of patient as it is unpleasant. Nicotinic acids dermatic formulations esters including propyl, benzyl or methyl nicotinate are the reason for the cause of dilatory effect in blood vessels. Effects of nicotinic acid on lipid metabolism are constant over a longer period of time , opposite to that flushing will have little tolerance , which results in flushing being reduced in few weeks.

Role of GPR109A Receptor in the Efficacy of Nicotinic Acid

Some studies which were done recently in a mice with deficiency of GPR109A demonstrated that flushing response due to nicotinic acid is mediated by nicotinic acid receptor [29]. Transplanting bone marrow in the GPR109A deficient animals helps with the response to nicotinic acid with cutaneous vasodilation [29]. This suggests that adipocytes are not the ones that mediates the flushing response, but the receptors on the bone marrow derived cells.Flushing response induced by nicotinic acid is induced with the activation of the receptor on epidermal immune cells and this is proved by the cutaneous reaction that has happened due to the application of skin permeable nicotinic acid esters, and this is indistinguishable from the nicotinic acid response induced by applying systematically. Another researcher has provided strong evidence in support to the fact that nicotinic acid flushing is strongly involved with epidermal Langerhans cells [30,31]. This fact is based on the observation that with increase in intracellular ca2+ along with the formation of proteinoids, Langerhans cells respond to nicotinic acid and express GPR109A. Another observation seen is, flushing response is not seen in the mice which are depleted of Langerhans cells [30,31].

It has been observed that without reducing the good effects of nicotinic acid , flushing response induced by nicotinic acid can be reduced with COX inhibitors. Prostanoids, like PGD2 or their metabolites are produced after administering nicotinic acid. It is clearly proved that nicotinic acid induced flushing response is mediated by PGD2 and and prostaglandin E2, which dilate dermal blood vessels via the activation of DP1 and EP2/EP4 receptors, form the studies of Pharmacological and genetic evidence. From these research data a nicotinic acid induced response model has emerged [32-37].

Increase in intracellular Ca2+ through the GPR109A activation on epidermal Langerhans cells is seen using nicotinic acid. As a result Ca2+ phospholipase A2 is activated and then arachidonic acid is formed which is then further metabolixed to PGD2 and prostaglandin E2. Both the prostanoids are now able to induce the diltion of blood vessels in the dermis upper layers through activation of Gi coupled receptors.

Conclusion: GPRA109 represents a molecular target that is exciting. Further examination of this receptor needs to be done inorder to understand mechanism of action of nicotinic acid and there by helping increase the therapeutic action of nicotinic acid. The recent studies have provided information on role of the receptor GPR109A in the therapeutic effects of nicotinic acid,but more research needs to be done to elevate the understanding of its role.

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